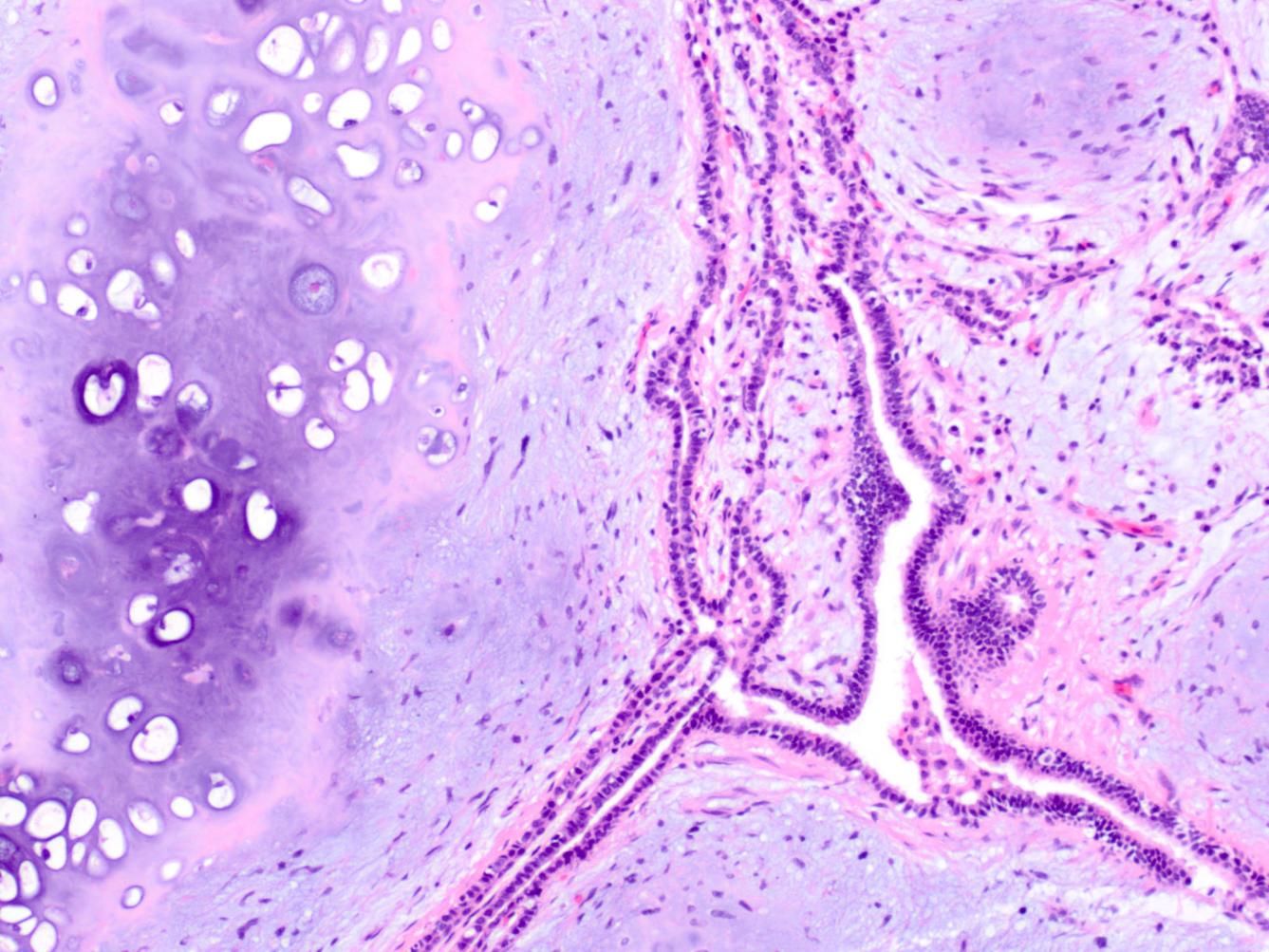
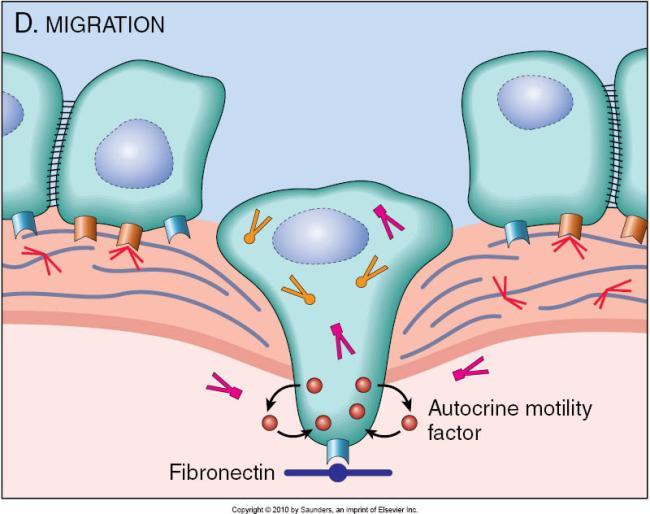
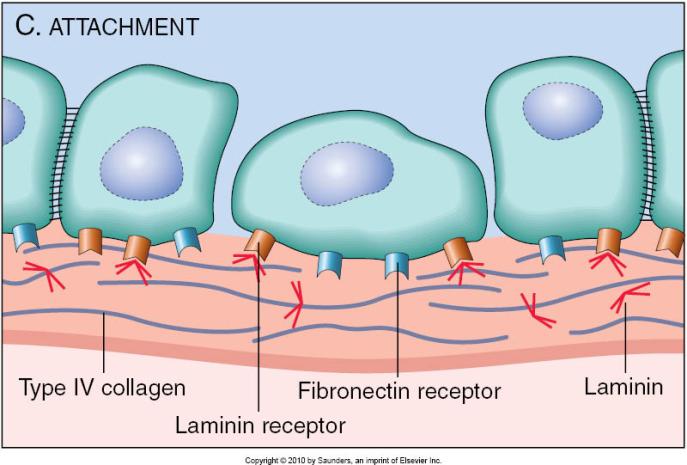
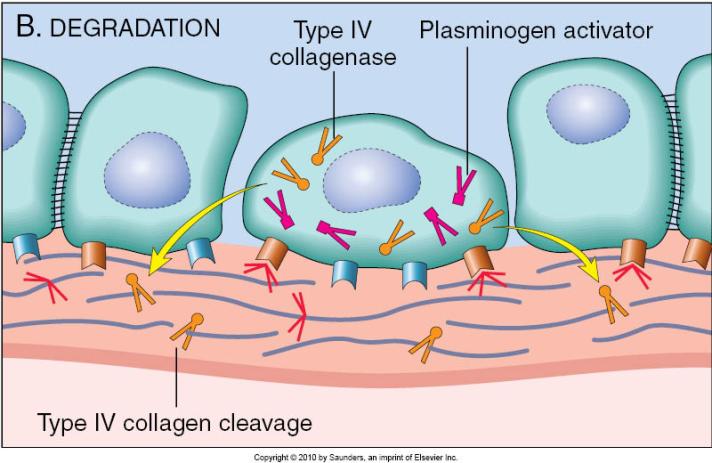
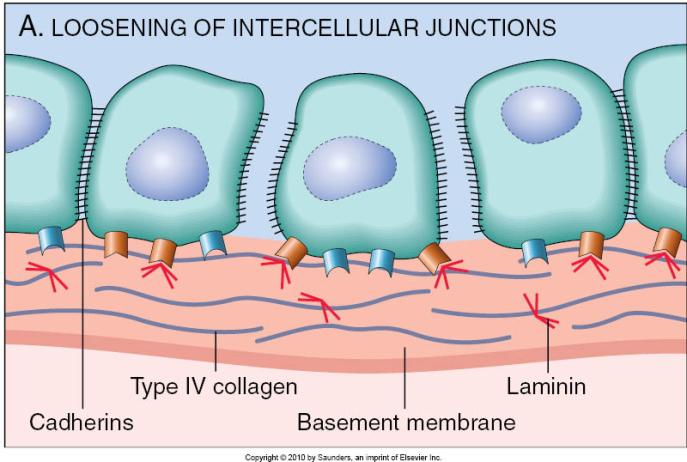
**NEOPLASIA OBJECTIVES**

* **Define the terminology of neoplasia.**
  + *Neoplasia* literally means “new growth”. The new growth is called a *neoplasm.*
  + Neoplasm
    - Abnormal mass of tissue, growth of which exceeds and is uncoordinated with normal tissues.
    - Growth persists in the same excessive manner after cessation of the stimuli which evoked the change.
    - This results from genetic alterations that are passed down to the progeny of the tumor cells.
    - These changes allow excessive and unregulated proliferation that becomes *autonomous*.
    - Entire population of malignant cells arises from a single cell that has incurred genetic damage = *clonal*
  + Hyperplasia – increase in the number of cells in an organ or tissue
    - Is a response to an exogenous stimulus
    - Responds to normal growth controls
    - However, hyperplasia can predispose to neoplasia as proliferating cells are more sensitive to carcinogens
  + Metaplasia
    - Replacement of one mature epithelium with another mature epithelium; adaptive response to stress
    - Not premalignant, but the injurious agent that led to metaplasia may predispose to malignant transformation
* **Distinguish the gross and microscopic features as well as biologic behavior of benign versus malignant neoplasms.** 
  + Benign
    - A neoplasm is said to be *benign* when its microscopic and gross characteristics imply that it will remain localized and not spread to other sites.
    - Nomenclature
      * **Benign tumors** – cell of origin + “oma”
        + Lipoma, chondroma, fibroma, angioma
        + Adenoma = benign epithelial neoplasm forming glands
        + Papilloma = benign epithelial neoplasm with finger-like warty projections
        + Cystadenomas = benign epithelial neoplasm forming large cystic masses
        + Polyp = neoplasm which produces a macroscopically visible projection above a mucosal surface and projects into a lumen
  + Malignant
    - The term *malignant* refers to a neoplasm in which the gross and microscopic features imply that it will invade, destroy adjacent structures, and spread to distant sites.
    - Nomenclature
      * Malignant = cancer
      * *Sarcoma* = malignant tumor arising in mesenchymal tissue
        + e.g. fibrosarcoma, liposarcoma, leiomyosarcoma, rhabdomyosarcoma, angiosarcoma
      * *Carcinoma* = malignant tumor of epithelial cell origin
        + e.g. adenocarcinoma, squamous cell carcinoma
      * *Teratoma*
        + Derived from >1 germ layer (totipotential cells)
        + Benign (mature), malignant, cystic
    - Mixed tumors
      * Divergent differentiation of a single clone along 2 lineages
        + e.g. pleomorphic adenoma, adenosarcoma, carcinosarcoma
    - *Hamartoma*
      * mass of disorganized but mature specialized cells indigenous to the particular site
      * Pulmonary Hamartoma
        + 
    - *Choristoma*
      * ectopic rest of normal tissue
    - Exceptions to naming rule:
      * Seminoma - malignant germ cell tumor
      * Melanoma - malignant tumor of melanocytes
      * Hepatoma (hepatocellular carcinoma) - malignant tumor of hepatocytes
      * Lymphoma – malignant tumor of lymphoid cells
  + Neoplasms are derived from cells that normally maintain a proliferative capacity.
* **Describe the clinical effects of cancer on the host.**
  + **Biologic hallmarks of malignancy**
    - The neoplasm must go through a sequential series of steps.
    - Each step is subject to many controls, therefore, at any point the breakaway cell may not survive.
    - 2 phases of *metastatic cascade*:
      * Invasion of extracellular matrix (ECM)
      * Vascular dissemination, homing of tumor cells and colonization
    - **Invasion of extracellular matrix (ECM)**
      * Detachment of tumor cells from each other
        + Family of glycoproteins - *cadherins* - involved in cell-cell adhesion
        + In several carcinomas, there is down-regulation of E-cadherin (reduces ability of cells to adhere to each other)
        + E-cadherins linked to cytoskeleton by *catenins*
      * Degradation of basement membrane and interstitial connective tissue
        + Secretion of proteases
      * Attachment to novel ECM components
        + Laminin, collagen IV, fibronectin
      * Migration of tumor cell to blood vessel (locomotion)
        + Complex multistep process
      * 
    - **Vascular Dissemination**
      * In blood vessel - cells are vulnerable
        + Survival in the circulation is enhanced by platelet-tumor aggregates (affords some protection)
        + Activation of coagulation factors – emboli
      * Extravasation from blood vessel
        + Involves adhesion to endothelium
      * Establishment of metastatic tumor related to:
        + Anatomic location of primary tumor
        + Natural pathways of drainage
        + Microenvironment of target tissue
* **Outline the general mechanisms of invasion and metastasis of malignant neoplasms.**
  + Differentiation of Benign and Malignant Tumors
    - **Differentiation and Anaplasia**
      * differentiation – degree to which tumor resembles the normal tissue, both morphologically and functionally.
        + An undifferentiated tumor is referred to as **ANAPLASTIC.**

Features of anaplasia:

Pleomorphism (cellular and nuclear)

Abnormal nuclear morphology

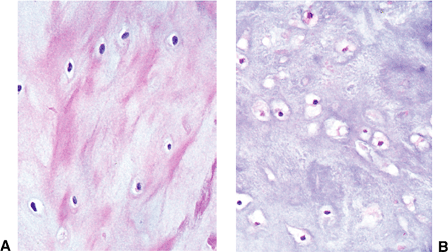
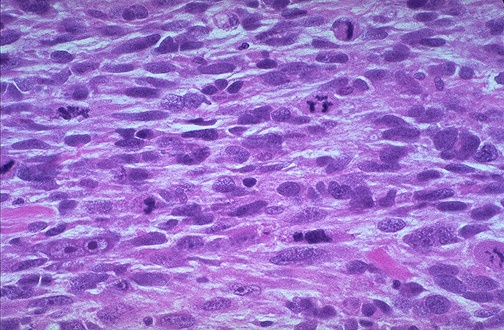
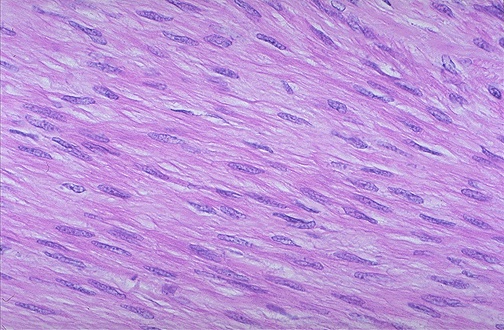
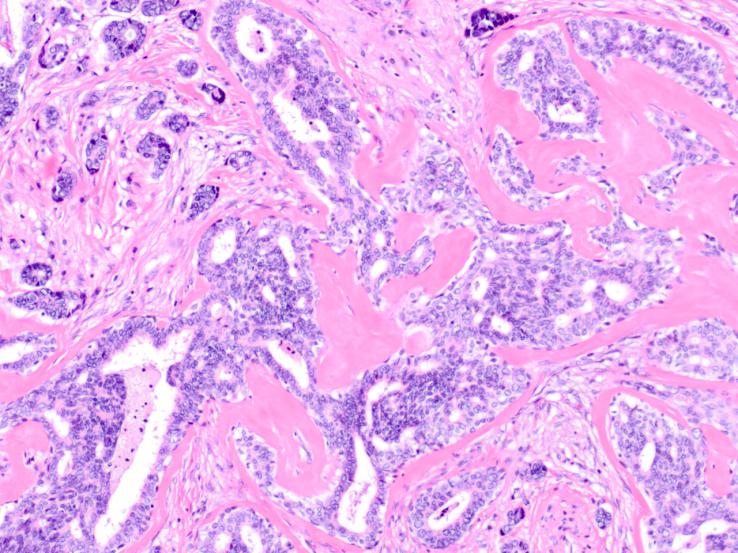
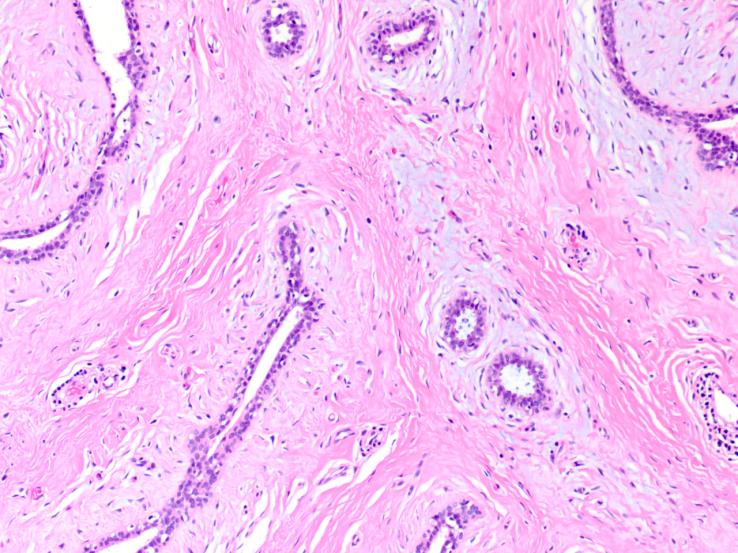
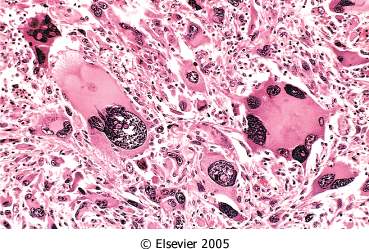
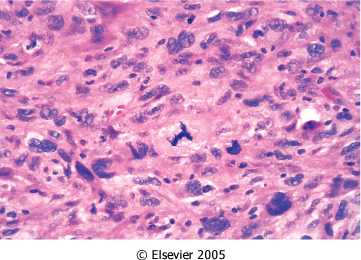
Mitoses\*

Loss of polarity

Other

Tumor giant cells

Necrosis

* + - * Extent to which neoplastic cells resemble comparable normal cells, morphologically and functionally
      * Benign neoplasms are well differentiated
      * Malignant neoplasms range from well differentiated to undifferentiated *(anaplastic)*
        + In between the two extremes are tumors that are commonly referred to as *moderately well differentiated.*
      * **
        + Benign chondroma (B) closely resembles normal cartilage (A).
      * 
        + Uterus - leiomyoma vs. leiomyosarcoma
      * 
        + Breast - benign fibroadenoma vs. infiltrating ductal carcinoma
      * 
        + Anaplastic tumors
    - **Functional changes**
      * The better the differentiation, the better it retains the functional capabilities found in its normal counterparts
      * Poorly differentiated and anaplastic carcinomas are unable to perform their normal functions
      * Sometimes abnormal functions emerge (production of hormones)
    - **Rate of Growth**
      * In general:
        + Most benign tumors grow slowly, whereas most cancers grow rapidly
        + The growth rate of tumors correlates with their level of differentiation
        + Rapid growth rate leads to tumor ischemia and necrosis.
        + Qualification\* - range of behavior is very wide
    - **Factors that influence tumor growth**
      * Kinetics of tumor cell growth
      * Tumor angiogenesis
      * Tumor progression and heterogeneity
      * ***Kinetics of Tumor Cell Growth***
        + Doubling time: The total cell cycle time for many tumors is equal to or longer than corresponding normal cells.
        + Growth fraction: Even in rapidly growing tumors, the fractions of cells replicating is only 20%; the rest are in G0 or G1. As tumors enlarge, growth fraction decreases. Why? ….lack of nutrients and oxygen.
        + Cell production and loss: Ultimately, the rate at which a tumor grows is determined by the excess of cell production over cell loss. The greater the imbalance, the more rapidly the tumor grows.
        + Clinical Implications:

Susceptibility to chemotherapy: Most anti-cancer agents act on dividing cells. Tumors with high growth fractions are most susceptible to anti-cancer agents.

Latent period of tumors = period of time before a tumor becomes clinically detectable (109 cells). In many cases is years.

* + - * ***Tumor Angiogenesis***
        + Tumors cannot grow beyond 1-2 mm in thickness unless they are vascularized, due to limitations in oxygen diffusion (hypoxia induces apoptosis).
        + Angiogenesis is a necessary correlate of malignancy.

Supplies oxygen and nutrients

New endothelial cells secrete growth factors that further stimulate tumor cell growth

Provides route for metastasis

* + - * + *Angiogenic switch –* involves increased production of angiogenic factors and loss of angiogenic inhibitors.

Factors produced by tumors themselves, inflammatory cells or stromal cells

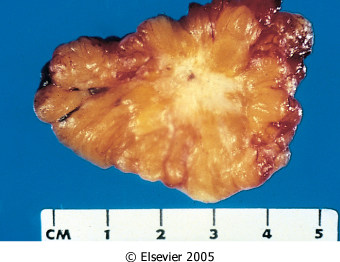
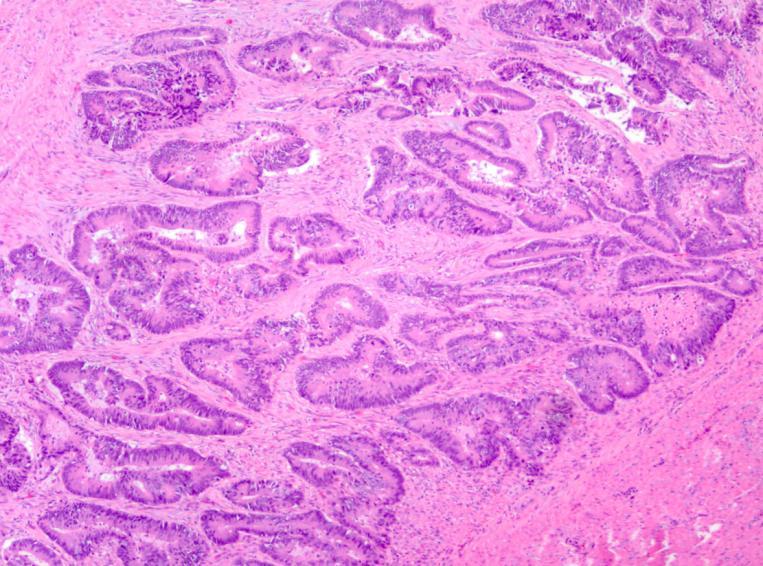
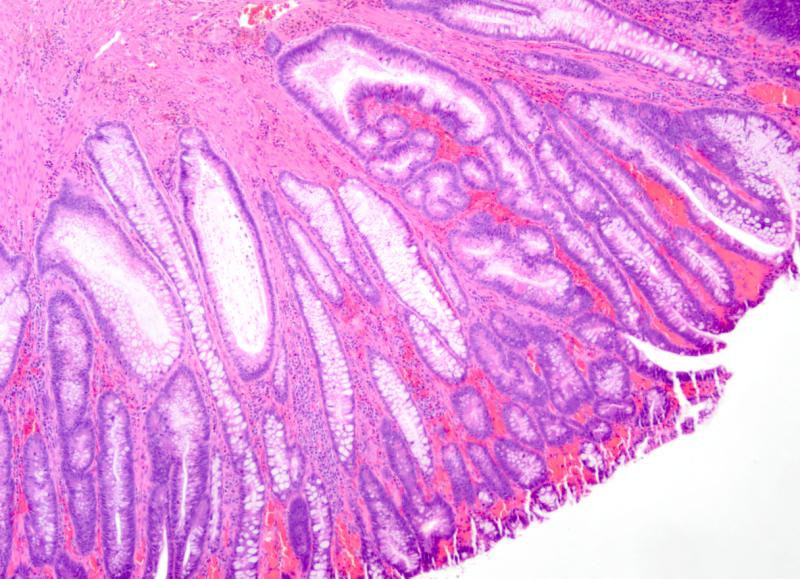
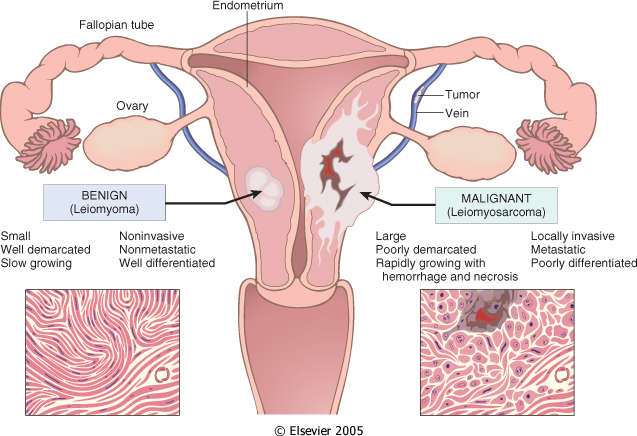
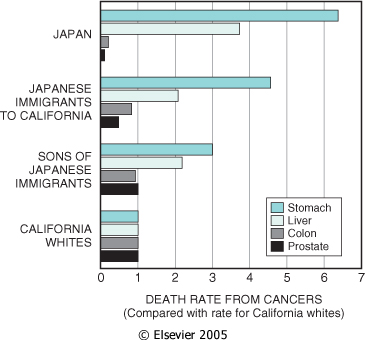
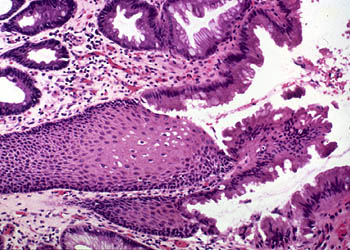
Controlled by several physiologic stimuli (eg. hypoxia)

* + - * + Blood vessels produced by tumors are **abnormal**.

Abnormal structure

Abnormal function

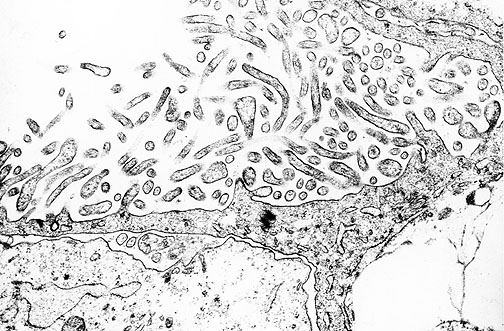
Unstable

* + - * ***Tumor Progression and Heterogeneity***
        + Tumor progression refers to the phenomenon in which there is sequential appearance within the tumor of subpopulations of cells that differ with respect to several phenotypic attributes, such as invasiveness, rate of growth, metastatic ability, karyotype, hormonal responsiveness and susceptibility to antineoplastic drugs.
        + Thus, although monoclonal, the constituent cells are relatively heterogeneous. *More on this in next lecture!*
        + Selects for cells that “beat the odds” (adept at survival, growth, invasion, metastasis).
        + Begins long before tumor is clinically evident.
    - **Local Invasion**
      * Benign tumors grow as cohesive expansile masses that remain localized to their site of origin
        + Because they grow slowly they usually develop a rim of compressed connective tissue (called a capsule)
        + Cause problems by impingement on other structures
      * Malignant tumors grow by infiltration and invasion of the surrounding tissue
        + Poorly demarcated from surrounding tissue (infiltrating border)
        + Next to metastasis, invasion is most reliable feature of malignancy
      * **Gross appearance - fibroadenoma vs. infiltrating ductal carcinoma**
        + ****
      * **Microscopic - colonic adenoma vs. invasive adenocarcinoma** 
        + ****
    - **Metastasis**
      * Metastasis unequivocally marks a tumor as malignant because benign tumors do not metastasize.
      * All cancers can metastasize except:
        + CNS gliomas
        + basal cell carcinomas
      * Pathways of spread
        + seeding of *body cavities* and surfaces, i.e. ovarian
        + *lymphatic spread* – most common route for carcinomas
        + *hematogenous spread* – typical of sarcomas but also carcinomas
      * **
  + Invasion and Metastasis are Multistep Events
    - Invasion of the basement membrane underlying the tumor.
    - Movement through extracellular matrix.
    - Penetration of vascular or lymphatic channels.
    - Survival and arrest of tumor cells within the vascular or lymphatic channel.
    - Extravasation from the circulation into a new tissue site.
    - Survival and growth as a metastasis, a process that involves angiogenesis.
* **Understand the role of epidemiologic and environmental factors in malignant neoplasms.** 
  + *Why study?*
    - Study of cancer patterns in populations can contribute substantially to knowledge about the origins of cancer
  + **Cancer Statistics**
    - Cancer death rate (U.S.A.) 565,650 in 2008
      * 23% of all deaths; 2nd leading cause of death (#1 is cardiovascular)
      * Incidence - 1,437,180 new cases in 2008
    - Women
      * Incidence: breast 26%, lung 14%, colorectal 10%
      * Deaths: lung 26%, breast 15%, colorectal 9%
    - Men
      * Incidence: prostate 25%, lung 15%, colorectal 10%
      * Deaths: lung 31%, prostate 10%, colorectal 8%
  + **Noteworthy Comparisons**
    - Over past 50 years, overall cancer death rate has increased in men and women but…
      * In men, since 1995, cancer incidence has stabilized and since 1990, death rate has decreased 18.4 %,
        + Due to decrease in death from lung, prostate and colorectal cancers.
      * In women, cancer incidence stabilized in 1995 and death rate has decreased 10.4% since 1991.
        + Due to decrease in death from breast and colorectal cancers
      * Lung cancer rates in women and intrahepatic bile duct cancers in men have increased significantly.
      * Deaths from primary liver cancers have doubled over the past 30 years (HCV).
  + Factors which affect cancer incidence
    - Geographic factors
    - Environmental exposures
    - Age
    - Genetics/heredity
    - Presence of precursor lesions
  + **Geographic & Environmental Factors**
    - Deaths from stomach cancer 7-8X higher in Japan than U.S.
    - Lung cancer death rate 2X higher in U.S. than Japan; Belgium even higher than U.S.
    - Skin cancer deaths (mostly melanomas) are 6X higher in New Zealand than Iceland
    - 
    - Obesity
    - Alcohol abuse - increases risk of carcinomas of the oropharynx, larynx, esophagus and liver
    - Cigarette smoking - implicated in cancer of the lungs, mouth, pharynx, larynx, esophagus, pancreas, bladder
    - Age of 1st intercourse, # partners - cervical cancer
    - UV, radiation, diet, viruses, medications (eg. methotrexate)
  + **Age**
    - For most cancers, increased age is associated with increased incidence.
    - Each age group has its own predilection:
    - <15 leukemias & lymphomas, neuroblastomas, Wilms tumors, retinoblastoma, bone & skeletal muscle (Ewing’s sarcoma, rhabdomyosarcoma)
    - 15-34 leukemia, breast, brain & NS, cervix, colon, soft tissue, NHL
    - 35-54 lung, breast, colon, ovary, cervix, brain & NS, NHL, pancreas
    - 55-74 lung, breast, colon, prostate, ovary, pancreas, NHL
  + **Heredity**
    - Autosomal dominant inherited cancer syndromes
      * Inheritance of a single mutant allele in cancer suppressor gene
      * Examples - childhood retinoblastoma, familial adenomatous polyposis (FAP), MEN syndromes, Neurofibromatosis I & II, Von Hippel-Lindau syndrome
      * Associated marker phenotype
    - Familial cancers
      * Familial clustering of specific forms of cancer but the transmission pattern is not clear
      * No marker phenotype
      * Familial forms of common cancers are recorded
        + Breast, ovary, colon, brain and others
    - Autosomal recessive syndromes of defective DNA repair
      * Xeroderma pigmentosum, Bloom syndrome, ataxia-telangiectasia
  + **Precursor Lesions to Invasive Cancer**
    - **Dysplasia**
      * Dysplasia = disordered maturation and organization within an epithelia
      * Risk of progression to cancer is related to severity.
      * Full thickness = CIS. Cytologically cells have the features of malignant cells, but do not invade into stroma – confined by BM.
      * In contrast to hyperplasia and metaplasia which are not premalignant.
      * Disruption of normal patterns of cellular maturation and organization in epithelia resulting in cytologic atypia of the dysplastic cells within the epithelium
      * Progression to cancer is not inevitable
      * Risk of progression to cancer increases with increasing severity of the dysplasia; e.g. CIN I, III, III - uterine cervix
    - When dysplasia involves the entire thickness of epithelium, but remains confined to the basement membrane, it is considered a preinvasive neoplasm and is referred to as **carcinoma in situ.**
      * High probability (but not inevitability) of progression to invasive carcinoma.
        + 70% cervical CIS progresses to invasive cancer in 12 years
      * Complete removal is usually curative
    - Dysplasia
      * 
  + **Nonhereditary Predisposing Conditions**
    - Cirrhosis of liver → hepatocellular carcinoma
    - Atrophic gastritis of pernicious anemia → stomach cancer
    - Chronic ulcerative colitis → colonic adenocarcinoma
    - Leukoplakia of oral and genital mucosa → squamous cell carcinoma
    - Hyperplasias and metaplasias - fertile soil
      * Endometrial hyperplasia
      * Bronchial mucosal metaplasia/dysplasia of smokers
      * Barrett’s metaplasia of esophagus
    - Metaplasia
      * 
  + **Other Precursor Lesions**
    - Certain forms of benign neoplasms
      * i.e. Colonic adenomatous polyps, esp. villous adenomas
      * 50% of villous adenomas develop cancerous change.
      * Early invasive carcinomas are associated with polyps.
      * Familial polyposis - 100% develop cancer by age 50.
      * Routine removal results in reduced risk.
      * Risk of invasive carcinoma is related to size histological type and degree of dysplasia in the polyp.
    - In general, the development of cancers in benign tumors is uncommon**.**
* **Given a patient scenario, select an appropriate laboratory method for making a cancer diagnosis.** 
  + **Clinical Features of Tumors**
    - Local and hormonal effects
    - Cancer cachexia
    - Paraneoplastic syndromes
  + *Local Effects of Tumor on Host*
    - Location and impingement on adjacent structures, i.e:
      * Pituitary adenoma - compression of normal gland leads to endocrinopathy
      * Benign or malignant GI neoplasms may cause obstruction
    - Functional activity, i.e. hormone synthesis (usually benign tumors of endocrine glands)
      * β-cell adenoma of pancreas <1 cm can cause fatal hypoglycemia
    - Bleeding and 2º infections when tumor ulcerates through natural surfaces
      * Erosive destructive growth or expansile pressure of benign tumor on natural surface
      * Melena and hematuria - GI and urinary tract
    - Acute symptoms caused by rupture or infarction
  + *Cancer Cachexia*
    - Progressive loss of body fat and lean body mass accompanied by profound weakness, anorexia and anemia
    - Equal loss of fat and muscle (contrast this to starvation)
    - Basal metabolic rate increased, despite reduced food intake
    - May be from cytokines produced by the tumor or by the host in response to the tumor
      * TNF-α, IL-1, IFN-γ
  + *Paraneoplastic Syndromes*
    - Symptom complexes in cancer patients that cannot be readily explained by either the local or distant spread of tumor or by elaboration of hormones indigenous to the tissue in which the tumor arose.
      * May be the earliest warning of a neoplasm
      * May cause significant clinical problems, even death
      * May mimic metastatic disease and confound treatment
    - Endocrinopathies
      * Cushing syndrome - secretion of ACTH or ACTH-like substance; *small cell carcinoma of lung* most common
      * Hypercalcemia - production of calcemic humoral substances by extraosseous neoplasms (PTHrP) secreted by *breast, lung (squamous), kidney, ovary*
    - Neuromyopathic
      * Peripheral neuropathies, cortical cerebellar degeneration, polymyopathy, myasthenia syndrome
      * Poorly understood
      * In some cases, antibodies induced against tumor cells that cross-react with neurons have been detected.
    - Acanthosis nigricans
      * Gray-black verrucous hyperkeratosis of skin
      * Appearance over 40 years - 50% malignancy
    - Hypertrophic osteoarthropathy *(1-10% of patients with bronchogenic carcinoma)*
      * Periosteal new bone formation at ends of long bones, metatarsals, metacarpals, proximal phalanges
      * Arthritis of adjacent joints
      * Clubbing of digits
    - Vascular and hematologic manifestations
      * Migratory thrombophlebitis
      * DIC
      * Nonbacterial thrombotic endocarditis
  + **Grading and Staging of Tumors** for treatment and prognosis
    - Grading
      * Histological estimate of the degree of differentiation
      * Well, moderately, poorly, undifferentiated, i.e. I, II, III, (IV)
      * Presumably correlates with aggressiveness
    - Staging
      * Severity of disease
      * Based on tumor size, extent of invasion, presence or absence of metastasis in nearby lymph nodes and distant organs
      * AJCC system is most common (called TNM system)
  + **Laboratory Diagnosis of Cancer**
    - Histologic and Cytologic Methods
      * Don’t underestimate the value and importance of clinical history!!
      * Samples must be adequate, representative, and well preserved.
      * Approaches:
        + Excision or biopsy

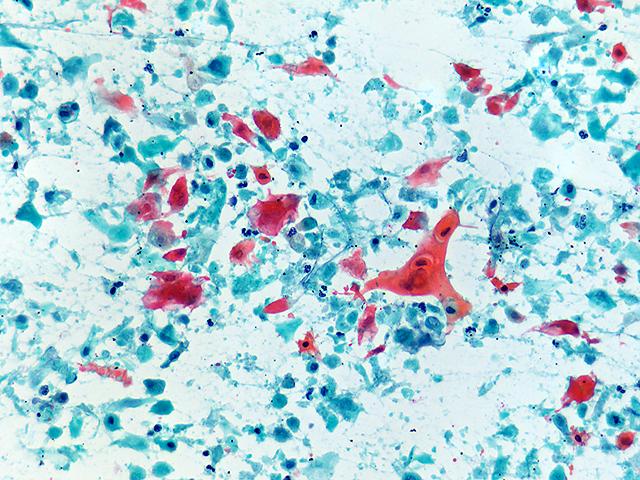
Routine paraffin embedded sections

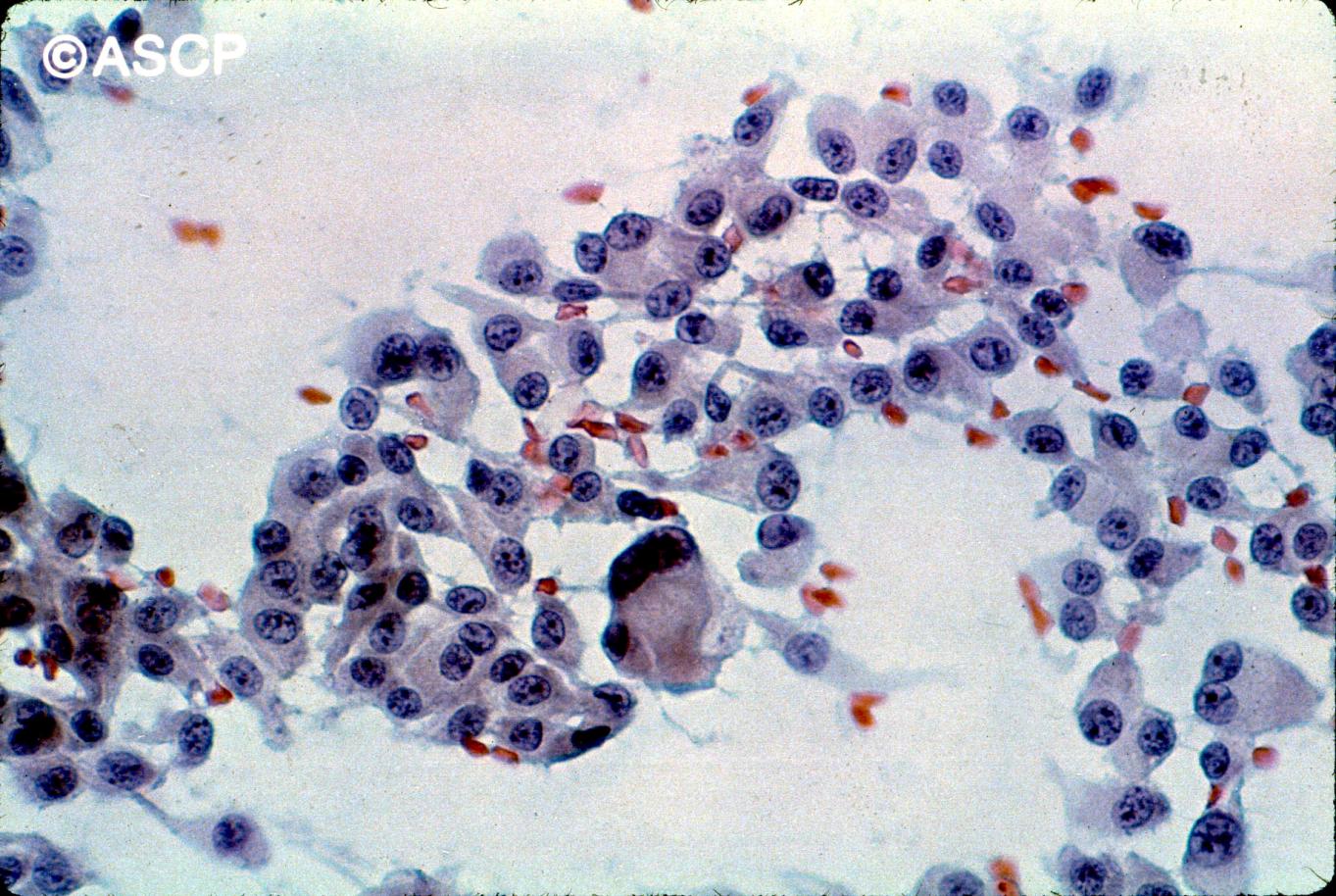
Frozen section

Electron microscopy



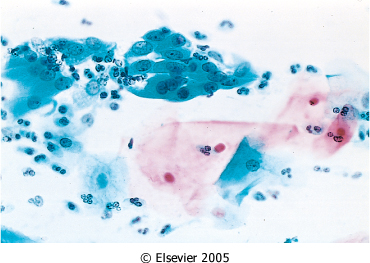
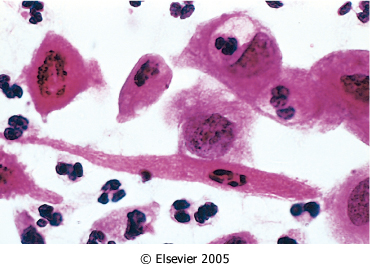
* + - * + Fine needle aspiration

🡨 Lung

🡨 Lymph Node

* + - * + Cytologic smears

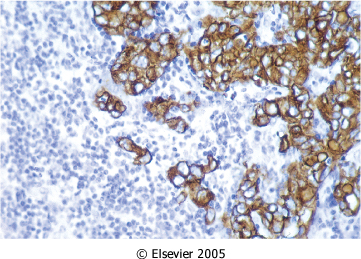
*Pap Smear*

** 

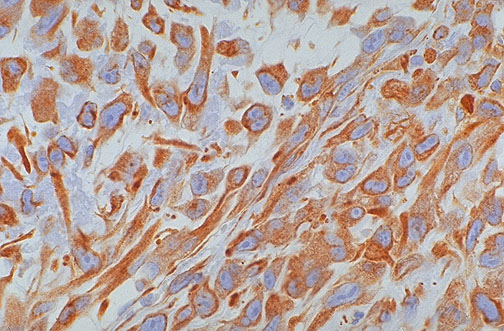
* + - Immunohistochemistry
      * Uses:
        + Categorization of undifferentiated or poorly differentiated tumors

Intermediate filaments: cytokeratins=carcinoma, desmin=muscle, vimentin

Cytokeratins



Vimentin



* + - * + Categorization of leukemias and lymphomas

T and B lymphocytes markers, mononuclear cells

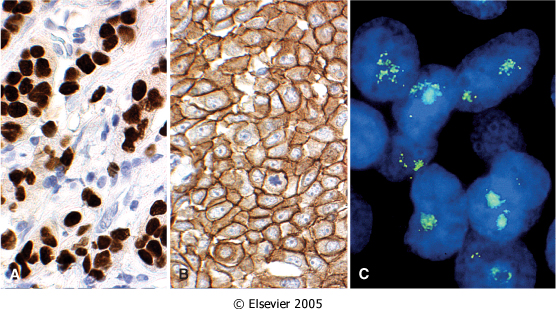
* + - * + Determination of site of origin of metastatic tumors

PSA, thyroglobulin, TTF-1, AFP, HMB-45, others

* + - * + Detection of molecules that have prognostic or therapeutic significance

Estrogen, progesterone receptors, *Her2/Neu (c-erbB2)*

ER Her2/neu Her2/neu FISH



* + - Flow cytometry
      * Main uses:
        + Identification of cell-surface antigens is widely used in the classification of leukemias and lymphomas
        + Now routine for specific diagnosis of subtypes of lymphoma
      * Detection of ploidy (DNA content) can be applied to specimens from a variety of sources
        + A relationship between abnormal DNA content (aneuploidy) and prognosis is becoming apparent for a variety of malignancies
    - Serum Tumor Markers
      * Biochemical indicators of the presence of a tumor
      * Not primary modalities
      * Helpful in supporting diagnosis, determining response to therapy and detecting relapse
      * Examples:
        + CEA (colon)
        + AFP
        + PSA
        + CA-125
    - Molecular Diagnosis
      * Nonlethal genetic damage lies at the heart of carcinogenesis.
      * Therefore, the key to understanding the origins of cancer and ultimately cure and prevent cancer lies in understanding its molecular and genetic basis.
      * Molecular diagnosis of cancer and the development of new diagnostic techniques is one of the fastest growing fields in medicine.